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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/467,901
Filing Date: December 21, 1999
Appellant(s): NEERVEN, JOOST VAN

Maryann T. Puglielli
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 07, 2006 appealing from the Office action mailed on September 08, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

Claim 15 is allowable.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,087,188	Johansen	11-2000
6,034,066	Johnson	03-2000

6,060,326	Frank	05-2000
6,004,745	Arnold, Jr. et al.	12-1999

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8-14, 16, 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) further in view of Johnson et al. (US 6,034,066) and Frank et al. (US 6,060,326).

Johansen et al. teach a method of detecting an antibody in a sample using a labeling compound and comprising the steps of mixing the ligand antigen, antibody or hapten bound to biotin with the sample; an antibody is directed against the antibody to be detected bound to a paramagnetic particles; and a chemiluminescent acridinium compound bound to avidin or streptavidin to form a solid phase complex; separating the solid phase from the liquid phase; and analyzing the separated solid phase for the presence of chemiluminescent complex. There are several embodiments. In one embodiment, the method comprises the following steps: mixing the ligand antigen,

antibody or hapten bound to biotin or a functional derivative thereof with the sample and the antibody directed against the antibody to be detected bound to paramagnetic particles to form a first solid phase complex; adding a chemiluminescent acridinium compound covalently bound to avidin, streptavidin or a functional derivative thereof to form a second solid phase complex; magnetically separating the solid phase from the liquid phase; initiating the chemiluminescent reaction, and analyzing the separated solid phase for the presence of the chemiluminescent complex. (see col. 3, line 30-col. 4, line 49). Johansen et al. also teaches the method for the quantification of specific antibodies, such as immunoglobulins, wherein a truly parallel reference immunoassay using an identical protocol as a reference. (see col. 5, lines 45-58). The method comprises measuring the concentration and/or the relative contents of a specific antibody in a liquid sample, wherein the measured light emission of a separated solid phase comprising a captured specific antibody coupled to a chemiluminescent label is compared with the measured light emission obtained in a parallel reference immunoassay wherein the total contents of the class of antibodies in the sample to which said specific antibody belongs is measured. (see col. 5, lines 50-60). The method comprising the steps of mixing a ligand antigen, hapten towards which the specific antibody to be measured is directly bound to biotin or a functional derivative thereof; an antibody directed against the constant portion of the antibody to be measured bound to paramagnetic particles and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof with the sample to form a first solid phase from the liquid phase; magnetically separating the first solid phase from the liquid

phase; initiating a chemiluminescent reaction and measuring the light emission of the separated first solid phase; mixing a ligand antibody directed against the class of antibodies to be measured bound to biotin or a functional derivative thereof ; an antibody directed against the constant portion of the class of antibodies to be measured bound to paramagnetic particles ; and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof wherein the term total shall mean the entire amount of the designated class of immunoglobulins (e.g. IgA, IgE, etc.) With the sample to form a second solid phase complex, magnetically separate the second solid phase form the liquid phase; initiating the light emission of the separated first solid phase with that of the separated second solid phase. (col. 3, lines 57-col. 4, line 31). The specific antibody to be measured in the sample is preferably a specific immunoglobulin selected from the group consisting of IgA, IgD, IgE, IgG, IgM and subclasses thereof. (See col. 3, line 30-col. 5, line 45).

However, Johansen et al. fails to teach using an IgE receptor to bind IgE antibody/ligand complexes and a method of quantification of IgE wherein the IgE to be detected is quantified using both CD23 alone to obtain a first measurement and using Fc.sub.epsilon.RII alone to obtain a second measurement. Johansen fails to teach a “method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody or a hapten in a liquid sample suspected to contain the IgE antibody by simulating in vivo interactions between IgE antibody, the IgE antibody’s ligand and the IgE antibody’s receptor”.

Johnson et al. teach multiple important roles of CD23 in the regulation of immune responses, particularly the regulation of IgE responses. Among these roles, CD23 acts as a cellular receptor for IgE and is found in various cell types including B cells. (See col. 1, line 31-col. 2, line 64).

Frank et al. teach detecting IgE antibodies using a human Fc epsilon receptor Fc.sub.epsilon.R. (See col. 1, line 45-col. 2, line 10).

It would have been obvious to one of ordinary skill in the art to use the IgE receptors of Johnson et al. and Frank et al. to measure IgE according to the method of Johansen et al. since both of these receptors, CD23 and Fc.sub.epsilon.R, are specific to IgE antibody and because Fc.sub.epsilon.R and CD23 can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. (See Frank et al. Col. 1, lines 19-34). Regarding claim 16, wherein the number of ligand molecules is between 100% and 200 % of the number of IgE molecules to be detected, it would have been obvious to one of ordinary skills in the art to use enough ligand molecules to optimize binding of all the IgE molecules to be detected. In order to detect 100% of the IgE present in the sample, at least 100% of ligand molecules must be present to bind all the IgE present in the sample. Regarding claim 23, since the combined references teach the same method steps as those of the claimed invention, such method would inherently simulate in vivo interactions between the IgE antibody, the ligand, and the IgE receptor.

Claims 6, 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) in view of Johnson et al. and Frank et al. (US 6,060,326) further in view of Arnold, Jr. et al. (US 6,004,745).

Johansen et al.,Johnson et al. and Frank et al. have been discussed above.

However, Johansen, Johnson and Frank fail to teach adding label after a first separation step and a second separation to separate the non-complexed labels.

Arnold, Jr. discusses in the background section that a typical sandwich assay involve incubating an immobilized antibody (IgE receptor) with a test medium (sample). Antigens, if in the medium, will bind to the antibody. After incubation, unbound antigen is removed in a separation step. After a second, or simultaneous incubation with a solution of labeled antibody, the bound antigen becomes sandwiched between the immobilized antibody and the labeled antibody. After a second separation step, the amount of labeled antibody can be determined as a measure of the antigen in the medium. (see col. 1, lines 55-66).

It would have been obvious to one of ordinary skill in the art to add the label molecule after a first separation step and then separating the non-complexed labels as discussed in Arnold, Jr. using the reagents in the method of Johansen modified by Johnson and Frank because such second separation steps, although time consuming, increases the sensitivity of the assay results. Furthermore, since the non-complexed immobilized antibody and the non-complexed labels are separated one at a time, cross-reactivity between the label and the immobilized antibody/reagent is eliminated.

(10) Response to Argument

Regarding the 103 rejection by Johansen in view of Johnson and Frank 2., Appellant submits that Johansen, who lacks the teaching of a IgE receptor, and Johnson's general teaching on the role of CD23 in the immune response do not invoke the specific concept of detecting IgE antibodies using IgE receptors. Frank 2, who teaches using Fc.sub.epsilon receptors for detecting IgG antibodies, does not motivate the skilled artisan to use a free dissolved ligand a carrier-bound IgE receptor. Thus, there is no guidance in these references that would allow the skilled artisan to arrive at the present invention.

Johansen teaches the generic assay steps of the present invention for detecting/quantifying IgE antibodies without using IgE receptor. Johnson teaches that CD23 is a IgE receptor that binds to IgE antibodies associated with allergic, anti-parasitic and chronic immune responses. (see Johnson col. 2, lines 26-30). One of ordinary skills in the art would use CD23 of Johnson in place of the capture antibody in Johansen, since Johansen teaches detecting IgE antibodies (see Johansen col. 4, lines 50-52), because Johnson teaches that CD23 can stimulate the production of IgE antibodies associated with allergic, anti-parasitic and chronic immune response. Thus, knowing that CD23 binds to IgE antibodies associated with allergic, anti-parasitic and chronic immune response, a skilled artisan can assess or detect the level of immune response by quantifying the amount of IgE using CD23. Frank teaches another example of IgE receptor, Fc.sub.epsilon.R, that binds to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. (see Frank col. 1, lines 19-34). Thus, one of ordinary skills in the art would be motivated to use either the receptors of Frank

or Johnson in the method of Johansen. Furthermore, since Johnson teaches that CD23 binds to cells such as B or T cells (see col. 1, lines 33-47), Frank teaches that Fc.sub.epsilon.R binds to mast cells, basophils and dendritic cells. (see col. 8, lines 42-48) and Johansen teaches using serum as the sample, such serum comprises all kinds of cells, one of ordinary skills in the art would be motivated to use both receptors of Frank and Johnson to detect IgE according to the method of Johansen to compare the abundance of a certain IgE in order to assess the allergic stage of a patient. CD23 influences antigen presentation to B and T lymphocytes, processes which determine the degree and nature of immune responsiveness to foreign antigens. (see col. 2, lines 5-15). Thus, one of ordinary skills in the art would assess the total IgE that binds to CD23 to study if there are B and T lymphocytes present in the serum sample. Using both receptors for one assay sample also eliminates extra time and effort comparing to carrying out separate assays for each receptor.

With regards to expectation of success, since Johansen teaches the same generic assay using an anti-IgE antibody as a capture reagent to capture or to bind to IgE in a serum sample, and Johnson and Frank teach using an IgE receptor, one of ordinary skills in the art would have reasonable expectation of success to replace the anti-IgE antibody with the IgE receptor knowing that the IgE receptor would bind with the IgE antibodies in serum. Frank teaches away from using an anti-IgE antibody to capture the IgE. Therefore, one of ordinary skills in the art would use the IgE receptor instead to capture the IgE because at least the Fc.sub.epsilon.R receptor would bind to IgE specifically without cross-reaction.

With regards to the canine IgE receptor vs. human receptors, this argument is irrelevant because the recited claims fail to specify canine receptor or human receptor.

With regards to the statement on page 13, last paragraph, of the appeal brief that Frank 2 makes it clear when it states "the present invention can include not only a Fc.sub.epsilon.R but also one or more additional antigens or antibodies useful in detecting IgE...examples of antibodies used in the present invention include antibodies that bind selectively to the constant region of an IgE antibody", Appellant argues that Johansen and Frank use different reagents.

Frank and Johansen do not have to use the same reagents. Indeed, if Frank uses the same reagents as those in Johansen, then Frank would anticipate the claimed invention.

With regards to the first citation of Frank 2, in the Office action dated April 6, 2005, which states that Frank relates to the discovery that purified, high affinity canine Fc epsilon receptor...can be used in canine epsilon immunoglobulin (IgE antibodies)-based detection...", Appellant also submits that "a general suggestion that an IgE receptor might be used in the genus detection assays does not suggest its use in the particular method of the invention.

In response, Appellant's invention fails to exclude a canine receptor. Appellant has not mentioned or recited any requirement that the IgE receptor must a human receptor. Thus, the canine IgE receptor in Frank 2 still applies. The present invention fails to recite whether a canine IgE or a human IgE is being detected. Therefore, the present invention is no different from a genus assay.

With regards to the citations about the receptor being attached to a substrate/particulate such as latex, polystyrene, nylon, nitrocellulose, agarose and magnetic resin. Suitable shapes include beads, well, plate, dipstick, celluloid type matrix, a magnetic particle and other particulates (see Frank 2, col. 10, lines 15-35, 50-60) of Frank 2, in the advisory action dated September 8, 2005, Appellant argues that the Office has not explained why out of this list, the artisan would be motivated to choose a particulate over a microtiter dish or dipstick.

Since Johansen teaches using a solid phase such as magnetic particles and Frank also suggests using a particulate support such as magnetic particles, one of ordinary skills in the art would be motivated to use magnetic particles to eliminate washing steps.

A reasonable expectation of success has been explained in the previous office action pages 9-10 and is once again established herein:

The motivation to combine the references has been clearly established in the previous office action. Johansen teaches a method for the quantification of specific antibodies such as immunoglobulins (IgE, IgA, ..). The sample containing the specific antibody is mixed with a ligand antigen (free dissolved ligand of the present invention); an antibody directed against a constant portion of the antibody to be measured bound to a paramagnetic particles and a chemiluminescent acridinium compound as a label; magnetically separating the bound from the unbound; and detect. Johnson uses a CD23 (a reagent directed against a constant portion of the antibody to be measured (IgE antibody)), which is specific for IgE antibody being detected. Frank teaches detecting

IgE antibodies using a human Fc epsilon receptor (Fc.sub.epsilon.R). Such Fc eplison receptor is specific to the IgE of the IgE antibody being detected. Thus, it would have been obvious to one of ordinary skill in the art to use CD23 or Fc.sub.epsilon.R as an IgE receptor to measure IgE antibody because these receptors can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. Regarding claim 16, it is obvious for an ordinary skill in the art to optimize the result by binding all the IgE molecules to be detected. Regarding Appellant's analysis of the two references about "solid supports vs. suspension of particles", it is well known that solid supports can include particles and Frank teaches that his reagents can be detected using particulate-based immunoassay (particulates such as magnetic particles, polystyrene, latex beads). Furthermore, whether a solid support or a particles is used, the antibody/ligand must bind to the solid support or a particle and a step of capturing must be performed. Thus, there is no difference between the reagents of the two methods.

Once again, Appellant fails to point out any factors that would prevent the combined references from having a reasonable expectation of success.

With regards to the limitation of "simulating an in vivo interaction" in claim 23, Applellant added in step (b) that "wherein the complexes that comprise the IgE antibody and the ligand are formed prior to contact with an IgE receptor to simulate in vivo interactions between the IgE antibody, the ligand, and the IgE receptor" and argues that this limitation is not obvious over the combined references.

Since the combination of Johansen, Frank 2, Johnson and Arnold teaches that the IgE antibody and the ligand are formed prior to contact with an IgE receptor, they

meet the requirement for simulating in vivo interactions between IgE antibody, the ligand and the IgE receptor because the newly added limitation merely requires that in order to simulate in vivo interactions, the IgE antibody and the ligand must form prior to contact with an IgE receptor.

Regarding the 103 rejection by Johansen in view of Frank 2 and Arnold, Appellant argues that Arnold does not cure the deficiency of motivation as discussed above. Arnold's method does not use an IgE receptor or mention the use of an IgE receptor. Rather, Arnold uses two antibodies, one immobilized to a surface and the other labeled. With respect to claims 17-19, the Office has not explained why one skilled artisan would replace only the immobilized antibody with an IgE receptor to arrive at the present invention instead of replacing both antibodies, which as alleged by the Office, may provide more specificity and sensitivity to the method.

Regarding the Arnold references, Appellant argues that Arnold's method does not use an IgE receptor or mention the use of an IgE receptor. Rather, Arnold uses two antibodies, one immobilized to a surface and the other labeled. The office has not explained why one skilled in the art would replace only the immobilized antibody with an IgE receptor to arrive at the invention instead of replacing both antibodies, may provide more specific and sensitive to the method. There is no teaching that such a single replacement would offer any particular advantage over a double replacement. Appellant also argues that the Office has not explained why one would be motivated to use two separation steps in the method of Johansen and Frank 2. Arnold also does not teach an assay that mimics in vivo interactions.

Arnold is relied upon for the second separation step. While a separation step is necessary and well known in the art in an assay after adding a reagent such as a carrier or a label to a mixture of samples containing the target compound, it is necessary to provide a reference that teaches such a separation step. While Johansen and Frank 2 both teach adding a label to the complex, they fail to teach a separation step to separate the unbound labels and the bound labels. However, one skilled in the art would know to carry out a second separation step in order to have meaningful results. Without a second separation step after adding a label, no meaningful detection can be done because not all the labels bind to the target. Furthermore, when using a label to detect a target compound, one would label the target compound directly. Thus, in the method of Johansen and Frank 2, the IgE is being detected, and thus the label must have some means to bind to the IgE. Such means is either an antibody against IgE such as one taught by Johansen or an IgE receptor taught by Frank 2. Either the IgE antibody or the IgE receptor would serve the same purpose that is to attach the label to IgE specifically. Thus, one of ordinary skills in the art would be able to figure out which reagent to use and would have a reasonable expectation of success to arrive at the present invention. Discussion of a single replacement of IgE receptor over a double replacement is unnecessary because Arnold is relied upon for the general teaching of using separation steps to separate bounds from unbound. Separation steps are known in the art for eliminating non-specific bindings, cross-reactivity and increasing sensitivity of the assay results. One of ordinary skills in the art would have been motivated to use two separation steps because the first separation is to eliminate non-bound carrier

(immobilized antibodies) and the second separation step is to eliminate non-bound labels. In any sandwich assay wherein the reagents (immobilized antibodies and then labels) are added one at a time, separation steps must be performed after each addition of each reagent (immobilized antibodies and labels). These separation steps are well known in the art.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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